

### **REMARKS/ARGUMENTS**

The foregoing amendments in the specification and claims are of a formal nature, and do not add new matter.

Prior to the present amendment, Claims 28-47 were pending in this application and were rejected on various grounds. With this amendment, Claims 28-32, 34-37 and 41-43 have been canceled without prejudice, Claims 33, 38-39 and 44 have been amended to clarify what Applicants have always regarded as their invention., and new Claims 48-53 have been added.

Claims 33, 38-40 and 44-53 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

The amendments to the specification and claims are fully supported by the specification and claims as originally filed and do not constitute new matter. In addition, new Claims 48-53 are fully supported by the specification as originally filed. Support for new Claims 48-53 can be found at least on page 139, lines 15-18, on page 140, lines 9-12, on page 282, lines 12-19 and on page 308, line 38 to page 309, line 7 of the specification.

Applicants thank the Examiner for entering the amendments of December 12, 2001, April 23, 2002, and September 9, 2002.

### **Specification**

In response to the Examiner's request, the specification has been amended to remove embedded hyperlink and/or other form of browser-executable code.

### **Oath/Declaration**

The Examiner alleges that the oath or declaration of the present application is defective because non-initialed and/or non-dated alteration have been made to the oath or declaration (for inventor Dan Eaton) and requires Applicants to submit a new oath or declaration in compliance with 37 C.F.R. §1.67(a). Applicants respectfully disagree.

Applicants respectfully submit that 37 C.F.R. §1.52(c)(1) states:

(c)(1) Any interlineations, erasure, cancellation or other alteration of the application papers filed must be made before the signing of any accompanying oath or declaration pursuant to §1.63 referring to those application papers and should be dated and initialed or signed by the applicant on the same sheet of paper. (Emphasis added).

Further, M.P.E.P. §605.04(a) states, "Any changes made in ink in the application or oath prior to signing should be initialed and dated by the applicants prior to execution of the oath or declaration." The previously submitted declaration included the change of address in ink by Dr. Dan Eaton. Dr. Eaton properly initialed below the change made to his address and dated the declaration. Therefore, Applicants respectfully submit that a new oath or declaration in compliance with 37 C.F.R. §1.67(a) is not required and request the Examiner to reconsider and withdraw the objection.

#### **Priority Determination**

The Examiner stated that the effective filing date for the application is December 7, 2001, the filing date of the present application.

Applicants disagree and submit that, as discussed below, Applicants rely on the gene amplification assay (Example 143) for patentable utility which was first disclosed in U.S. Provisional Application Serial No. 60/141,037, filed June 23, 1999, priority to which has been claimed in this application. Accordingly, the present application is entitled to at least the June 23, 1999 priority for subject matter defined in Claims 33, 38-40 and 44-53.

#### **Claim Rejections Under 35 U.S.C. §101 and §112, First Paragraph**

Claims 28-47 are rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

Claims 28-47 are also rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility ..., one skilled in the art would not know how to use the claimed invention".

In particular, the Examiner asserts that "[t]he instant specification discloses no data for

any activity of the nucleic acid of SEQ ID NO:276." The Examiner specifically notes that the asserted utility that the polypeptide of SEQ ID NO:277 has semaphoring biological activity is not substantial and specific because "[t]he art teaches that structural similarity in semaphorin protein is not predictive of functional similarity." The Examiner further notes that "[t]he instant specification does not disclose any specific disease, condition, or disorder state wherein there is a change in expression levels, forms, or activity of the polypeptide of the SEQ ID NO:277." The Examiner then concludes that "[s]ince significant further experimentation would be required to determine how to use the polypeptide of SEQ ID NO:277 as a therapeutic agent, the asserted utility is not substantial."

The Examiner finally asserts that "[t]he specification does not reasonably provide enablement for all variants of the PRO1317 polypeptide because the claims "[f]ail to recite any structural or functional limitation," and the art establishes "[t]he unpredictability of the effects of mutation on protein structure and function."

Applicants respectfully disagree with and traverse the above rejections.

Applicants submit that the cancellation of Claims 28-32, 34-37 and 41-43 renders the rejection of these claims moot. Claims 33, 38-40 and 44-53 have patentable utility for the reasons discussed below.

### **Legal Standard**

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1574). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1580); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1577).

Compliance with 35 U.S.C. §101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1583) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a

*preponderance of the totality of the evidence* under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that *it is more likely than not* that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, shifts the burden of rebuttal to the applicant. The issue will then be decided on the totality of evidence.

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient*, at least with regard to defining a "substantial" utility." M.P.E.P. §2107.01, emphasis added. Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. §2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." M.P.E.P. §2107 II(B)(1)(ii). Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Revised Interim Utility Guidelines Training Materials, 1999.

**Proper Application of the Legal Standard**

Applicants submit that the invention defined by the presently amended claims has specific, substantial and credible utility for the claimed polynucleotides.

The Examiner asserts that "[t]he instant specification discloses no data for any activity of the nucleic acid of SEQ ID NO:276." The Examiner further notes that "[t]he instant specification does not disclose any specific disease, condition, or disorder state wherein there is a change in expression levels, forms, or activity of the polypeptide of the SEQ ID NO:277."

Applicants disagree and submit that Example 143 explicitly discloses the biological activity of the nucleic acid SEQ ID NO:276, that is, the nucleic acid of SEQ ID NO:276 is amplified in lung tumor and is a diagnostic marker for lung cancer.

As discussed above, Applicants rely on the gene amplification data for priority and to establish patentable utility for the PRO1317 polypeptide. This data was first disclosed in Provisional Application Serial No. 60/141,037, filed June 23, 1999, the priority of which is claimed in the present application. Hence, the effective filing date of the present application is June 23, 1999 for subject matter of the instant claims defined in Claims 33, 38-40 and 44-53.

Gene amplification is an essential mechanism for oncogene activation. The gene amplification assay is well-described in Example 143 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 8, including primary lung and colon tumors of the type and stage indicated in Table 7. As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was

pooled and used as a control. Gene amplification was monitored using real-time quantitative TaqMan PCR. Table 8 shows the resulting gene amplification data. Further, Example 143 explains that the results of TaqMan™ PCR are reported in  $\Delta C_t$  units, wherein one unit corresponds to one PCR cycle or approximately a 2-fold amplification relative to control, two units correspond to 4-fold amplification, 3 units to 8-fold amplification etc. The specification discloses that the nucleic acids encoding PRO1317 had  $\Delta C_t$  value of  $> 1.0$ , which is **more than 2-fold increase**, for primary lung tumors LT1, LT1a, LT9, LT10, LT15, LT17 and LT22. PRO1317 showed approximately 1.15 to 2.69  $\Delta C_t$  unit which corresponds to  $2^{1.15}$  to  $2^{2.69}$  - fold amplification or 2.219 to 6.453 fold amplification in primary lung tumors.

Because amplification of DNA71166-1685 occurs in various tumors, it is likely associated with tumor formation and/or growth. As a result, antagonists (*e.g.*, antibodies) directed against PRO1317 would be expected to be useful in cancer therapy.

It is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis.

In support, Applicants submit a Declaration by Dr. Audrey Goddard with this response and particularly draw the Examiner's attention to page 3 of the declaration which clearly states that:

It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

The attached Declaration by Audrey Goddard clearly establishes that the TaqMan real-time PCR method described in Example 143 has gained wide recognition for its versatility,

sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO1317 is *a diagnostic marker of human lung cancer*.

Applicants respectfully submit a Declaration by Dr. Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the present application, to demonstrate the credibility of the gene amplification assay. In particular, Dr. Ashkenazi is in opinion that gene amplification of a gene, whether by aneuploidy or any other mechanism, is still useful as a diagnostic marker. As a result, the present gene amplification assay is a well-controlled experiment and give rise to data of biological significance. As Dr. Ashkenazi explains,

An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Applicants further submit that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level.

Applicants first submit exemplary articles to show that the art indicates that, generally, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. For example, Orntoft *et al.* (Mol. and Cell. Proteomics, 2002, Vol.1, pages 37-45) studied transcript levels of 5600 genes in malignant bladder cancers many of which were linked to the gain or loss of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (Cancer Res., 2002, Vol. 62, pages 6240-45) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene

expression levels." (see page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.*, (PNAS, 2002, Vol. 99, pages 12963-12968) who studied a series of primary human breast tumors and showed that "...62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

In addition, enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations, they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that,

for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology, that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the vast majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis Declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1317 gene, that the PRO1317 protein is concomitantly overexpressed. Thus, Applicants submit that the PRO1317 proteins and nucleic acids have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the protein for diagnosis of cancer.

Applicants further submit that even if one assumes *arguendo* that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer would still have a specific and substantial utility. In support, Applicants particularly draw the Examiner's attention to page 2 of the Declaration by Dr. Ashkenazi which explains that,

even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein,

is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient with agents that target that gene product. This not only saves money, but also the patient need not be exposed to the side effects associated with such agents.

This is further supported by the teachings of the attached article by Hanna and Mornin. (Oathology Associates Medical Laboratories, August (1999), copy enclosed). The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Examiner alleges that "[s]ince significant further experimentation would be required to determine how to use the polypeptide of SEQ ID NO:277 as a therapeutic agent, the asserted utility is not substantial."

As discussed above, the Utility Guidelines caution Office personnel to be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the substantial, or "real world" utility prong of the utility requirement. The data shown in the present application clearly demonstrates that the nucleic acid of SEQ ID NO:277 that encodes PRO1317 is amplified in lung cancer. Based on this information one skilled in the art at the effective priority date of this application would have accepted that the nucleic acid encoding PRO1317 meets the utility requirement of the 35 U.S.C. §101 as a diagnostic marker for cancer.

The Examiner specifically notes that the asserted utility that the polypeptide of SEQ ID NO:277 has semaphoring biological activity is not substantial and specific because "[t]he art

teaches that structural similarity in semaphorin protein is not predictive of functional similarity."

As discussed above, Applicants rely on the gene amplification data disclosed in Example 143 to establish the patentable utility.

The Examiner finally asserts that "the specification does not reasonably provide enablement for all variants of the PRO1317 polynucleotide" because "the specific activities of the protein of SEQ ID NO:277 and the assays to test for its activity, are not disclosed" and "there is not discussion, or working examples disclosed in the instant case, as to what amino acids are necessary to maintain the functional characteristics of the claimed PRO1317 polypeptides". The Examiner also asserts that "[t]he specification does not reasonably provide enablement for all variants of the PRO1317 polynucleotide claims "[f]ail to recite any structural or functional limitation," and the art establishes "[t]he unpredictability of the effects of mutation on protein structure and function."

Without acceding to the Examiner's rejection, Claims 28-32 have been canceled without prejudice. The cancellation renders the rejection moot. None of the remaining claims recite the variants of the PRO1317. Accordingly the rejection should be withdrawn.

In view of the above, Applicants have demonstrated a credible, specific and substantial asserted utility for the nucleotides encoding the PRO1317 polypeptide. Further, based on this utility and the disclosure in the specification, one skilled in the art would know how to use the claimed polynucleotides at the time of filing. Applicants respectfully request the Examiner to reconsider and withdraw the rejection of under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

**Claim Rejection Under 35 U.S.C. §112, First Paragraph (Written Description)**

Claims 28-47 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of sufficient written description.

Without acquiescing to the Examiner's position in the current rejections, and without prejudice to further prosecution of the subject-matter in one or more continuation or divisional applications, Applicants submit that the cancellation of Claims 28-32, 34-37 and 41-43 renders

the rejection of these claims moot.

None of the remaining claims recite the variants and fragments of the PRO1317 polypeptide. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

**Claim Rejections – 35 U.S.C. §112, Second Paragraph**

Claims 28-33, 35-37, 41 and 43 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleges that because of the phrase "extracellular domain", the metes and bounds of claims are indefinite in view of the instant specification.

Applicants submit that the cancellation of Claims 28-32, 35-37 and 41-43 renders the rejection of these claims moot.

Furthermore, since the term "extracellular domain" is no longer present in Claim 33 (and, as a consequence, those claims dependent from the same), the rejection is believed to be moot, and should be withdrawn.

**Claim Rejections – 35 U.S.C. §102**

Claims 28-43 are rejected under 35 U.S.C. § 102(a) as being anticipated by McCarthy *et al.* (WO 00/77239), with a publication date of December 21, 2000. The Examiner alleges that McCarthy *et al.* disclose a polypeptide that is 100% identical to the polypeptide of SEQ ID NO: 277.

As discussed above, the pending claims of the instant application are entitled to the effective filing date of June 23, 1999, and hence, the publication by McCarthy *et al.* is not a prior art under 102(a) since its publication date is after the effective priority date of this application. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection under 35 U.S.C. §102(a).


**CONCLUSION**

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C59**)

Respectfully submitted

Date: December 20, 2004

By:   
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